INTERNAL MEDICINE

□ CASE REPORT □

Acute Thrombocytopenia after Initiating Anticoagulation with Rivaroxaban

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Abstract

A 75-year-old man with paroxysmal atrial fibrillation developed a traumatic intracranial hemorrhage during warfarin treatment. The administration of warfarin was stopped and rivaroxaban therapy, a novel oral anticoagulant (NOAC), was started. Immediately, his platelet count decreased to $3.7\times10^4/\mu L$. The platelet count recovered rapidly after cessation of rivaroxaban administration. Development of thrombocytopenia and its rapid recovery was observed again after another administration, and subsequent cessation, of the drug. A diagnosis of rivaroxaban-induced thrombocytopenia was made. The incidence of thrombocytopenia due to NOACs is rare. Careful attention to thrombocytopenia, which is associated with a higher risk for life-threatening bleeding, is therefore necessary during treatment with NOACs.

Key words: drug-induced thrombocytopenia, rivaroxaban, novel oral anticoagulants

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Introduction

Novel oral anticoagulants (NOACs), such as dabigatran, rivaroxaban and apixaban, are administrated for patients with non-valvular atrial fibrillation (NVAF) to prevent stroke. NOAC is superior to warfarin in ease of use and efficacy in randomized controlled trials (1-3). Furthermore, the risk of intracranial bleeding is strongly decreased in patients treated with NOACs compared with warfarin. Therefore, NOACs are superior to warfarin in NVAF patients with a high risk of intracranial bleeding. We herein present a patient who developed severe thrombocytopenia soon after receiving rivaroxaban treatment. Thrombocytopenia during anticoagulation is a high risk for life-threatening bleeding. Careful attention not only to bleeding, but also to thrombocytopenia, after initiating rivaroxaban treatment is therefore necessary.

Case Report

A 75-year-old man with paroxysmal atrial fibrillation developed a traumatic intracranial hemorrhage during warfarin treatment for the prevention of stroke. The patient was taking aspirin for ischemic heart disease; warfarin for paroxysmal atrial fibrillation; and amlodipine, telmisartan, pravastatin, furosemide, trichlormethiazide and famotidine. The day before hospitalization, the patient fell down at home and sustained a head contusion. The following day he felt general malaise and was transferred to our hospital.

On admission, the patient's level of consciousness was abnormal [Japan coma scale 100; Glasgow coma scale 11 (E1, V4, M6)]; his height was 163 cm and his weight was 40.2 kg. His body temperature was 36.3℃, pulse 85 beats/min and regular, and blood pressure was 181/77 mmHg. A physical examination revealed ecchymoma of the right temporal region of his head. A neurological examination revealed left hemiplegia [left upper limb manual muscle test (MMT), 2/5; left lower limb MMT, 3/5]. There were no other obvious neurological findings. Laboratory studies indicated a white blood cell (WBC) count of 8,500/μL, a red blood cell (RBC) count of $281\times10^4/\mu L$, a hemoglobin (Hb) level of 9.3 g/dL, a hematocrit (Ht) level of 27.3%, a platelet count of $16.8\times10^4/\mu L$, a total protein level of 6.7 g/dL,

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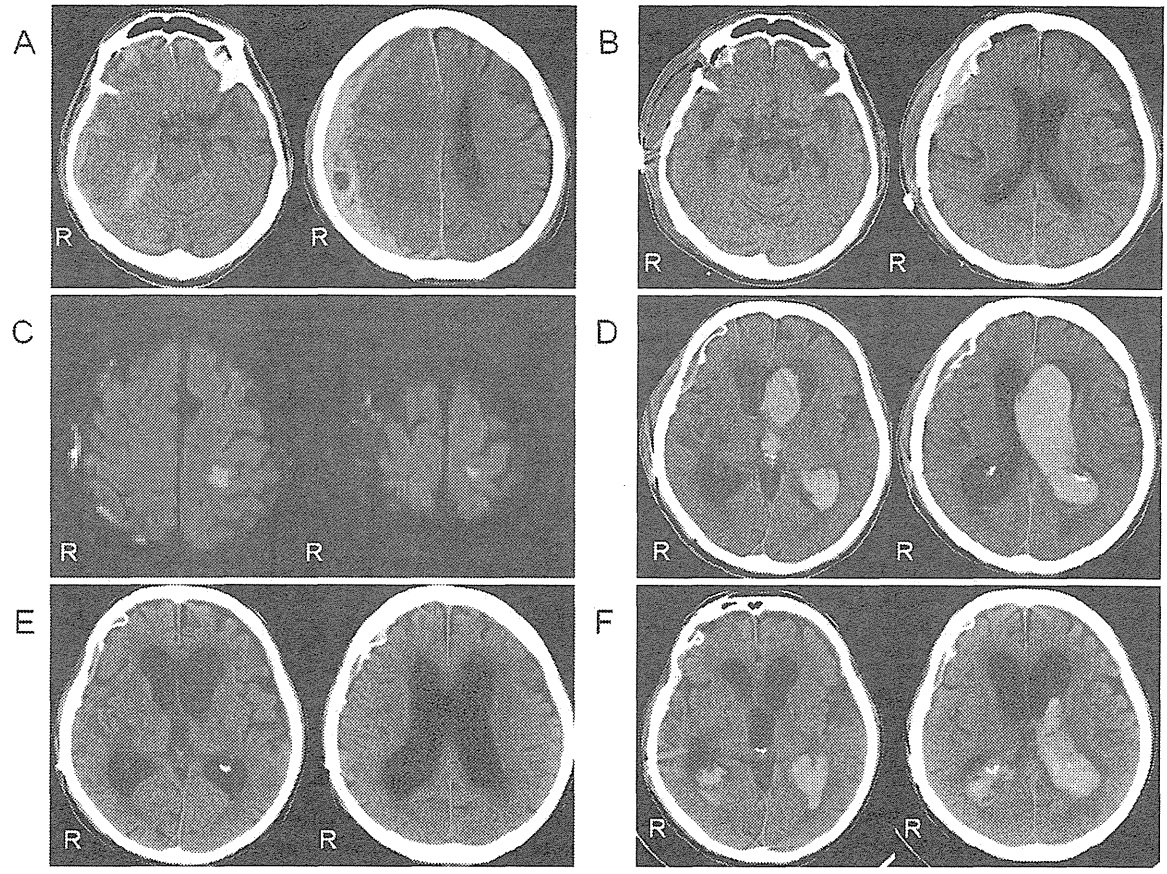

Figure 1. **Head computed tomography (CT) and head magnetic resonance imaging (MRI) during hospitalization. (A) Head CT on admission revealed an acute subdural hematoma and brain contusion in the right frontal lobe. (B) Head CT on day 36, the day following cranioplasty, showed that the intracranial hemorrhage did not recur. (C) Head diffusion-weighted MRI on day 51 revealed an acute brain infarction. (D) Head CT on day 61 revealed an intraventricular hemorrhage with hydrocephalus. (E) The intraventricular hemorrhage improved by day 120. (F) However, the intraventricular hemorrhage recurred at day 137.**

an albumin level of 3.4 g/dL, a blood urea nitrogen level of 33 mg/dL, a serum creatinine level of 1.4 mg/dL, a creatinine clearance level of 25.9 mL/min and a total cholesterol level of 149 mg/dL. The Na level was 141 mmol/L, the K level was 4.4 mmol/L, the Cl level was 107 mmol/L, the aspartate aminotransferase (AST) level was 23 U/L, and the alanine aminotransferase (ALT) level was 17 U/L. The lactate dehydrogenase (LDH) level was 195 IU/L, the creatine phosphokinase level was 70 IU/L, the total bilirubin (T-bil.) level was 0.3 mg/dL, the plasma glucose level was 273 mg/dL, and the glycosylated hemoglobin level was 6.2%. The C-reactive protein (CRP) level was 0.52 mg/dL. The prothrombin time-international normalized ratio (PT-INR) was 1.90 and the activated partial thromboplastin time (APTT) was 25.9 seconds.

On head computed tomography (CT) scan, an extensive acute subdural hematoma was seen from the right frontal to parietal region, and a partial cerebral contusion was seen in the right frontal lobe (Fig. 1A). On a head magnetic resonance imaging (MRI) scan, there were no findings to suggest either malignant disease or vascular disease as the cause of the intracranial hemorrhage.

On the first day of admission, 500 units of coagulation factor IX complex and 10 mg of menatetrenone (vitamin K complex) were immediately administered for rapid correction of the PT-INR. A decrease in the PT-INR from 1.90 to 1.43 was confirmed, and cerebral decompression and hematoma evacuation were performed via craniotomy on the same day. After confirming that there was no recurrence of bleeding on hospital day 3, warfarin administration for atrial fibrillation was restarted. Later, warfarin was discontinued on hospital day 22 due to a scheduled cranioplasty and continuous heparin infusion was started. Cranioplasty was performed on hospital day 35 (Fig. 1B). On day 51, right hemiplegia was noted and a head MRI scan showed acute infarction in the left frontal lobe cortex (Fig. 1C), after which no marked changes in the patient's neurological symptoms were seen. However, when a follow-up head CT scan was conducted on day 61, an acute intraventricular hemorrhage was seen in the left lateral ventricle together with moderate to severe hydrocephalus (Fig. 1D). At that time the APTT was 41.0 seconds (1.6 times that on admission). Continuous

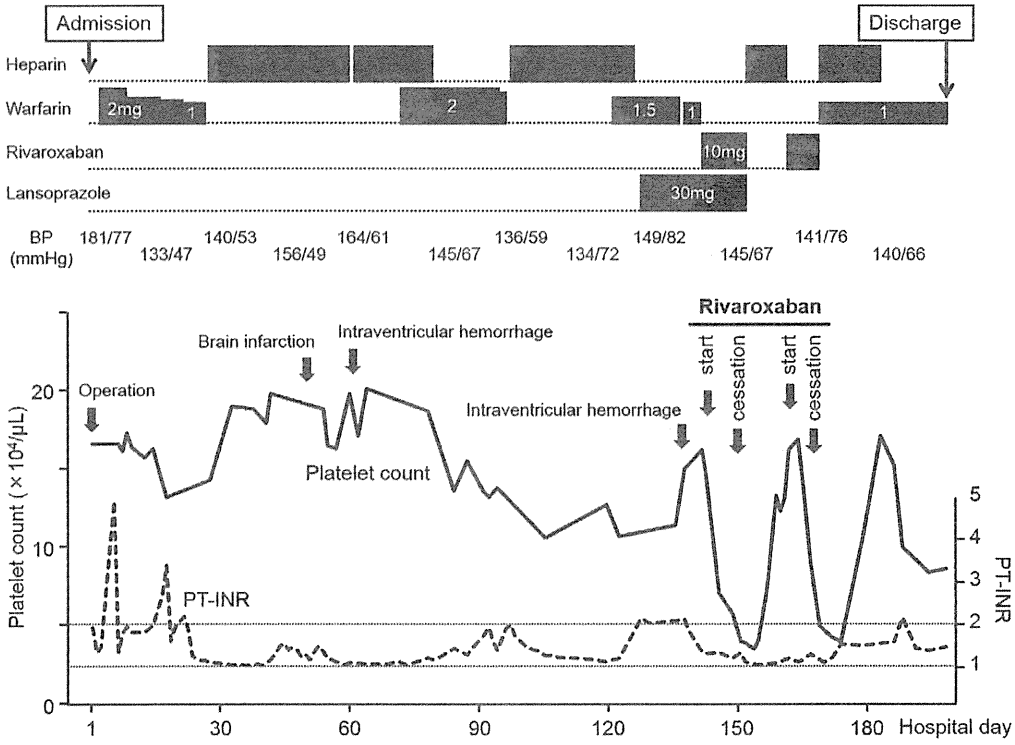

Figure 2. Platelet counts, prothrombin time-international normalized ratio (PT-INR), and key clinical events during hospitalization. Note: The patient had a normal baseline platelet count. The administration of rivaroxaban through a nasogastric tube was started 143 days after admission. The platelet count decreased to $3.7\times10^4/\mu L$, and rivaroxaban was discontinued 8 days after initiation. The platelet count completely normalized by 11 days after cessation of rivaroxaban administration. At 163 days after admission, administration of rivaroxaban was restarted. The acute thrombocytopenia recurred but recovered rapidly after cessation of rivaroxaban administration.

heparin infusion was discontinued and, following heparin neutralization with the administration of protamine, endoscopic hematoma evacuation was performed on the same day. After confirming that there was no recurrence of bleeding postoperatively, heparin was restarted at a lower dose on day 62. There was no recurrence of bleeding even after restarting heparin, and on day 76, administration of warfarin (2 mg) was restarted via a nasogastric tube. The dose was adjusted to a target PT-INR of 1.6-2.0 in consideration of the bleeding risk. Heparin administration was later ceased, but a gastrostomy was scheduled, so warfarin was discontinued and continuous heparin infusion was restarted on day 96. The gastrostomy was performed on day 109. On a head CT scan done on day 120 (Fig. 1E), the intraventricular hematoma had resolved. Therefore, on day 121, administration of warfarin (1.5 mg) was restarted, and on day 126 the administration of heparin was terminated. After warfarin was restarted, the PT-INR stabilized at around 2.0 with 1.5 mg of warfarin. However, on day 137 there was a recurrence of the intraventricular hemorrhage (Fig. 1F). At that time the PT-INR was 2.10. The blood pressure during this course fluctuated in the range of 120-140/60-80 mmHg with administration of antihypertensive agents (telmisartan, 40 mg; amlodipine, 5 mg; furosemide, 40 mg; and trichlormethiazide, 1 mg) (Fig. 2). Warfarin administration for the recurrent intraventricular hemorrhage was temporarily discontinued, and it was confirmed that there was no exacerbation in the intraventricular hemorrhage. Warfarin administration (1 mg) was then restarted on day 139. However, due to the multiple complications attributed to warfarin therapy since admission, we switched the patient to rivaroxaban, a NOAC for which administration as a suspension via tube is reported to be valid (1). NOACs are associated with less intracranial bleeding than warfarin (2-5). Warfarin was discontinued on day 143, and rivaroxaban (10 mg) was started, after which the platelet count decreased to $7.3\times10^4/\mu L$ on day 145 (third day after the start of rivaroxaban). On day 150 (eighth day after the start of rivaroxaban), the platelet count had fallen to $3.7\times10^4/\mu L$. Because there were no findings that suggested abnormalities in the coagulation or fibrinolytic system or blood cell disorders (WBC count of 4,700/μL, RBC count of $281\times10^4/\mu L$, a reticulocyte level of 9.6‰, Hb level of 9.3 g/dL, Ht level of 27.3%, T-bil. level of 0.3 mg/dL, LDH level of 195 IU/L, PT-INR 1.02, APTT 37.5 sec, fibrin/fibrinogen degradation products (FDP) level of 5.9, D-dimer level of 1.2, and a fibrinogen level of 265), the patient's thrombocytopenia was strongly suspected to be drug-induced. On hospital day 150, the drugs being administered

Table. Reports of Thrombocytopenia due to Oral Anticoagulants

	Drug information	Interview form (frequency)	Post-marketing Surveillance (the number of incident / all Patients)
Dabigatran	described	0.3%	16 / about 7,000
Rivaroxaban	not described	0.2% [3]	none / about 20,000
Apixaban	described	0.2% [2]	1 / about 8,000
Warfarin	not described	not described	—

The incidence of thrombocytopenia during anticoagulation with novel oral anticoagulants was reported to be low.

were furosemide (40 mg), valproic acid (1,200 mg), Fluitran (1 mg), telmisartan (40 mg), amlodipine (5 mg), pravastatin (5 mg), rivaroxaban (10 mg), and lansoprazole (30 mg). These drugs had been administered from before admission or from day 1 in the hospital with the exception of rivaroxaban and lansoprazole. Therefore, the newly added rivaroxaban and lansoprazole (starting on day 128) were discontinued as suspected offending drugs, and the patient was switched to continuous heparin infusion. On hospital day 153 (third day after cessation), the platelet count decreased to $3.7\times10^4/\mu L$ but rapidly recovered afterward. On day 161 (11th day after cessation), the platelet count was $16.4\times10^4/\mu L$. At that time we considered the possibility that rivaroxaban was causing the thrombocytopenia, since thrombocytopenia was not listed as an adverse effect on the rivaroxaban package insert (6). We hypothesized that it was most likely the lansoprazole that had caused the thrombocytopenia (7). Considering the cardiogenic cerebral embolism that occurred during hospitalization, the subsequent difficulty in anticoagulation therapy with warfarin, and that rivaroxaban is an agent that can be administered in a suspension via a tube, rivaroxaban was restarted on day 163. However, the platelet count decreased again to $5.2\times10^4/\mu L$ on day 168 (sixth day after restart) and so rivaroxaban was considered to be the offending drug and discontinued. Afterward, the platelet count rapidly improved to $17.3\times10^4/\mu L$ on day 182 (13th day after cessation) (Fig. 2).

The plan for subsequent anticoagulation therapy was to use warfarin with careful dose adjustments, and on hospital day 198, the patient was transferred to a rehabilitation hospital for convalescence. During that course, there was no gastrointestinal bleeding or appearance of purpura or hematoma, and a lymphocyte transformation test performed on day 173 was negative for rivaroxaban.

Discussion

The mechanism of thrombocytopenia due to rivaroxaban is currently unknown. In the present case, the patient had no cell disorders other than thrombocytopenia. Furthermore, once treatment with rivaroxaban was stopped, the platelet count rapidly recovered and there were no findings that suggested increased platelet consumption. Therefore, the thrombocytopenia seen was likely drug-induced and may be the result of drug-dependent antibody production (8, 9). The frequency of thrombocytopenia caused by NOACs appears low (2-4). However, because thrombocytopenia during anticoagulation may be associated with a higher risk of life-threatening bleeding, clinicians should monitor for the development of thrombocytopenia at the initiation of NOAC treatment.

Although there are no reports of thrombocytopenia due to warfarin use, there are reports of thrombocytopenia with NOAC use, albeit at a low frequency (Table). The package insert in Japan for rivaroxaban as of November 2013, which was administered to the present patient, did not mention thrombocytopenia (6). However, 3 of 1,280 patients (0.2%) enrolled in the J-ROCKET AF study were noted as having thrombocytopenia (4). While its frequency is low, thrombocytopenia is thought to be an adverse effect common to NOACs. The criteria for assessing whether or not thrombocytopenia is caused by pharmaceutical products have not been established in Japan. When the USA criteria for assessing thrombocytopenia (10) were applied to this patient, he met the conditions for Level 1: definitive and was diagnosed with thrombocytopenia due to rivaroxaban. The onset mechanism for drug-induced thrombocytopenia is generally: (1) suppressed production of platelets, (2) platelet phagocytosis or general increased consumption, and (3) increased immunological platelet destruction (9). The mechanism of thrombocytopenia due to rivaroxaban and other NOACs is unknown, but in this patient, there were no cell disorders other than thrombocytopenia. Furthermore, when rivaroxaban was stopped, the platelet count increased and there were no findings that suggested increased platelet consumption. Considering these findings, drug-induced thrombocytopenia in this patient was most likely due to the production of drug-dependent antibodies (8). In this mechanism, the drug, by binding reversibly with platelet membrane proteins, induces structural changes in the membrane proteins resulting in new antigen exposure. Since thrombocytopenia is elicited by the production of antibodies to these new antigens, verification of platelet antibodies is necessary.

We have described a case in which acute thrombocytopenia was diagnosed after the administration of rivaroxaban. Thrombocytopenia during the administration of NOACs may lead to severe hemorrhage considering that it occurs during anticoagulation therapy. When introducing an NOAC, measurement of the creatinine clearance and hemoglobin levels for the early detection of an occult hemorrhage is recommended. Changes in the platelet count must be carefully monitored while NOACs are being used in order to avoid hemorrhagic complications.

The authors state that they have no Conflict of Interest (COI).

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Clinical Science

Significance of plasma adiponectin for diagnosis, neurological severity and functional outcome in ischemic stroke — Research for Biomarkers in Ischemic Stroke (REBIOS)

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ABSTRACT

Objective. Although adiponectin is a major adipocytokine that affects the pathogenesis of various cardiovascular diseases, its clinical significance in stroke remains controversial. We investigated the clinical significance of plasma adiponectin for the diagnosis, neurological severity and functional outcomes of patients with ischemic stroke.

Methods. We prospectively enrolled 171 patients with ischemic stroke and 171 age- and sex-matched healthy controls. Blood samples and clinical information were obtained at day 0, 3, 7, 14 and 90 after stroke onset.

Results. Average adiponectin values at day 0 did not significantly differ between the controls and the patients, but were significantly lower and higher in patients with atherothrombotic brain (ATBI) ($p = 0.047$) and cardioembolic (CE) ($p = 0.008$) infarction, respectively, than in the controls. Multivariate logistic regression analyses showed that the adiponectin value at day 0 could predict ATBI (odds ratio, 0.75; 95% confidence interval, 0.58 to 0.91, $p = 0.009$, per 1-μg/mL increase). Adiponectin values at day 0 were positively associated with neurological severity as evaluated by the National Institute of Health Stroke

Abbreviations: AF, Atrial fibrillation; ATBI, atherothrombotic brain infarction; CE, cardioembolic infarction; CHF, chronic heart failure; CI, confidence interval; CT, computed tomography; HDL-cholesterol, high density lipoprotein-cholesterol; IQR, interquartile range; LAC, lacunar infarction; LDL-cholesterol, low density lipoprotein-cholesterol; MetS, metabolic syndrome; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; OR, odds ratio; SD, standard deviation; SE, standard error; TOAST, Trial of Org 10172 in Acute Stroke Treatment; NIHSS, National Institute of Health Stroke Scale; UC, unclassified type of brain infarction.

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Scale upon admission (r = 0.420, p = 0.003) and were higher in the groups with poor outcomes (modified Rankin Scale (mRS) ≥ 3 on day 90) than in those with good ones (mRS ≤ 2) in all stroke subtypes, with statistical significance in ATBI (p = 0.015).

Conclusions. Plasma adiponectin values may help to classify stroke subtypes and predict neurological severity and functional outcome in ischemic stroke patients.

1. Introduction

Adiponectin is the most abundant circulating adipocytokine secreted from the adipose tissue and plays an important role in glucose and lipid metabolism, vascular biology and energy homeostasis [1,2]. These effects of adiponectin improve insulin resistance [3], systemic inflammation [4] and endothelial function [5], thus preventing the development and progression of atherosclerosis and subsequent cardiovascular diseases [6].

Several studies have shown the association of low plasma adiponectin levels with the development of ischemic heart diseases [7–9]. Adiponectin apparently suppresses the development of ischemic heart diseases. However, whether plasma adiponectin levels are associated with the development of ischemic stroke remains controversial [10]. Although a previous case–control study demonstrated the association of hypoadiponectinemia with ischemic stroke [11], other studies did not found the association [6,12]: in particular, a recent large prospective study of 3885 middle-aged men over a period of 27 years demonstrated that plasma adiponectin values did not predict risk of stroke events [13]. However, we speculate that this controversy might be due in part to the heterogeneous mechanisms of ischemic stroke, compared with ischemic heart disease. Ischemic stroke includes not only atherothrombotic infarction that has a similar pathogenesis to ischemic heart disease, but also lacunar infarction, cardioembolic infarction and other stroke types. Indeed, previous studies examining adiponectin values in stroke patients did not take stroke subtypes into consideration.

In the present study, we prospectively recruited patients with ischemic stroke, categorized them according to stroke subtypes and examined the temporal profiles of plasma adiponectin values to determine their significance in ischemic stroke. We also compared plasma adiponectin values between the patients and age- and sex-matched healthy controls, and assessed the associations between plasma adiponectin values and neurological severity/functional outcomes in the patients.

2. Methods

2.1. Patients

We enrolled stroke patients from the Fukuoka Stroke Registry (FSR), a multicenter, prospective cohort study of patients with acute stroke. Over 90% of patients admitted to one of the seven clinical stroke centers in Fukuoka, Japan have participated in the FSR. Detailed information about the registry is available elsewhere [14,15].

The objectives, study design, risks and benefits for the Research for Biomarkers in Ischemic Stroke (REBIOS) study were explained in detail to each patient upon admission or to family members. The inclusion criteria were as follows: hospitalized within 24 h of the onset of ischemic stroke, definitive diagnosis of stroke subtype, written informed consent to participate provided by the patient or when consciousness was disturbed, a surrogate. Patients with the following complications were excluded from the study: severe infection, malignancy, anemia and chronic inflammatory diseases. The participating patients were prospectively enrolled and followed up until 3 months after onset. We recruited patients with ischemic stroke who were hospitalized at Kyushu University Hospital, National Hospital Organization Kyushu Medical Center or St. Mary's Hospital between November 2007 and April 2010. The local ethics committee at each hospital approved the REBIOS study design.

Age- and sex-matched controls (n = 171) without a history of cardiovascular diseases, such as stroke, coronary heart diseases and atrial fibrillation, were selected from the healthy individuals who participated in the Hisayama Study, a prospective cohort study that started at 1961 in the town of Hisayama, Japan [16].

2.2. Diagnosis of ischemic stroke and subtype

Stroke was defined as the sudden onset of a non-convulsive and focal neurological deficit persisting for over 24 h. Brain infarction diagnosed by brain imaging, including computed tomography (CT) and magnetic resonance imaging (MRI), in all patients was classified as atherothrombotic brain (ATBI), cardioembolic (CE) or lacunar (LAC) infarction, and unclassified (UC) based upon the diagnostic criteria of the Classification of Cerebrovascular Disease III proposed by the National Institute of Neurological Disorders and Stroke [17], and of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) study [18]. Ischemic stroke was classified with reference to detailed clinical features, hematological results and findings of electrocardiography, transthoracic and transesophageal echocardiography, carotid duplex imaging, transcranial color-coded Doppler sonography and cerebral angiography.

2.3. Data sampling

Peripheral venous blood samples were collected from patients at day 0 (within 24 h), 3, 7, 14 and 90 after stroke onset. Blood samples were collected into tubes containing EDTA and plasma separated by centrifugation was stored at −80 °C. In healthy individuals, blood samples were collected only at the time of enrollment in the study. Plasma adiponectin and insulin values were determined by HumanMAP® v 1.6 multiplex immunoassays (Rules-Based Medicine, Austin, TX, USA).

2.4. Risk factors

Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic pressure ≥ 90 mmHg or as currently medicated with antihypertensive drugs during the chronic stage of stroke or at enrollment for controls. Diabetes mellitus was determined by either a 75-g oral glucose tolerance test according to the diagnostic criteria of the World Health Organization in 1998 [19], casual blood glucose levels (≥11.1 mmol/L), or a medical history of diabetes. Dyslipidemia was defined as total cholesterol ≥ 5.7 mmol/L, low density lipoprotein-cholesterol ≥ 3.62 mmol/L, high density lipoprotein-cholesterol < 1.03 mmol/L or under current therapy with cholesterol-lowering drugs. Atrial fibrillation (AF) was diagnosed based on electrocardiographic findings or medical history. Smoking was defined as having a previous or current smoking habit and alcohol intake as consumption including occasional drinking. We investigated the frequency of metabolic syndrome (MetS) and how it influenced adiponectin values [20,21]. Pre-stroke administrations of antithrombotic, antihypertensive, antihypercholesterolemic and antidiabetic agents were also assessed.

2.5. Evaluation of neurological severity and functional outcome

In order to examine the association between plasma adiponectin values and neurological severity, we assigned the patients to quartiles (Q1 (mild) to Q4 (severe)) based on National Institute of Health Stroke Scale (NIHSS) scores upon admission in each stroke subtype. We evaluated functional outcomes by modified Rankin Scale (mRS) scores at day 90, and classified into two groups: patients with mRS ≥ 3 as poor outcome group and those with mRS ≤ 2 as good one.

2.6. Statistical analysis

Data are presented as means ± SD, means ± SE, number (%), or as medians with interquartile ranges (IQR). Categorical variables were compared by univariate analysis using the chi-square test. Continuous variables were compared using an unpaired Student's t-test or multiple comparisons as appropriate. $P < 0.05$ was considered to represent a significant difference. We identified independent predictors for a diagnosis of stroke subtype using a multivariate logistic regression analysis with adjustments for age, sex and other variables that significantly ($p < 0.05$) or marginally ($p < 0.1$) differed in the univariate analyses. All data were analyzed using JMP software ver.9 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Background characteristics of controls and patients with stroke

Table 1 summarizes the background clinical characteristics of 171 patients with stroke and controls, and shows that plasma adiponectin values did not significantly differ between the two groups (3.8 ± 0.2 (controls) vs. 3.9 ± 0.2 μg/mL (patients), p = 0.836; Table 1 and Fig. 1A).

Table 1 – Background characteristics of controls and patients with stroke.

	Controls n = 171	Patients n = 171	P
Baseline characteristics			
Age, y	68.1 ± 10.1	68.3 ± 10.1	0.843
Sex: male, n (%)	115 (67.3)	115 (67.3)	1.000
Body mass index, kg/m^2	23.3 ± 2.8	23.6 ± 3.8	0.295
Risk Factors			
Smoking, n (%)	36 (21.1)	96 (56.1)	<0.001
Alcohol, n (%)	98 (57.3)	75 (43.9)	0.013
Hypertension, n (%)	72 (42.1)	132 (77.2)	<0.001
Dyslipidemia, n (%)	88 (51.5)	100 (58.5)	0.196
Diabetes mellitus, n (%)	11 (6.4)	54 (31.6)	<0.001
Atrial fibrillation, n (%)	0 (0)	59 (34.5)	<0.001
Laboratory Data			
Adiponectin, μg/mL	3.8 ± 0.2	3.9 ± 0.2	0.836
LDL cholesterol, mg/dL	139 ± 28	118 ± 30	<0.001
HDL cholesterol, mg/dL	63 ± 17	53 ± 13	<0.001
Triglycerides, mg/dL	122 ± 61	119 ± 77	0.716
HbA1c, %	5.1 ± 0.3	6.1 ± 1.5	<0.001
Insulin, μU/mL	1.6 ± 1.0	4.2 ± 5.4	<0.001

Data are means ± SD for age, body mass index, LDL-cholesterol, HDL-cholesterol, Triglycerides, HbA1c, Insulin, and number (%) for other variables.

3.2. Adiponectin values according to medications administered to patients

Table 2 shows adiponectin values with respect to medications administered to the patients. We found significant differences in plasma adiponectin values between patients medicated with and without β-blockers (2.7 ± 0.6 vs. 4.1 ± 0.2 μg/mL, p =0.046), diuretics (6.2 ± 0.6 vs. 3.5 ± 0.2 μg/mL, p < 0.001), or thiazolidinedione (6.3 ± 1.2 vs. 3.8 ± 0.2 μg/mL, p = 0.048).

3.3. Differences in plasma adiponectin values among stroke subtypes

We classified the 171 patients with ischemic stroke into 4 subtypes, ATBI (n = 34; 19.9%), LAC (n = 45; 26.3%), CE (n =49; 28.7%) and UC (n = 43; 25.1%), and compared their plasma adiponectin values at day 0 with those of the controls. Plasma adiponectin values were significantly lower in the patients with ATBI (2.7 ± 0.5 μg/mL, p = 0.047) and higher in those with CE (5.3 ± 0.5 μg/mL, p = 0.008) than in the controls (3.8 ± 0.2 μg/mL) (Fig. 1B).

We also investigated adiponectin levels in patients with or without metabolic syndrome (MetS), and found no significant differences between patients with and without MetS in total stroke and each stroke subtype (Table 3).

A multivariate logistic regression analysis adjusted for age, sex, smoking habit, alcohol intake, hypertension, diabetes mellitus, atrial fibrillation and neurological severity (NIHSS upon admission) identified the plasma adiponectin value at day 0 as an independent predictor of ATBI (odds ratio [OR] 0.75, 95% confidence interval [CI] 0.58 to 0.91, p = 0.009, per 1 μg/mL increase; Fig. 1C). In contrast, the multivariate analysis showed that high plasma adiponectin values tended to predict CE without statistical significance (OR, 1.11; 95% CI, 0.91 to 1.39, per 1 μg/mL increase; Fig. 1C). However, the plasma

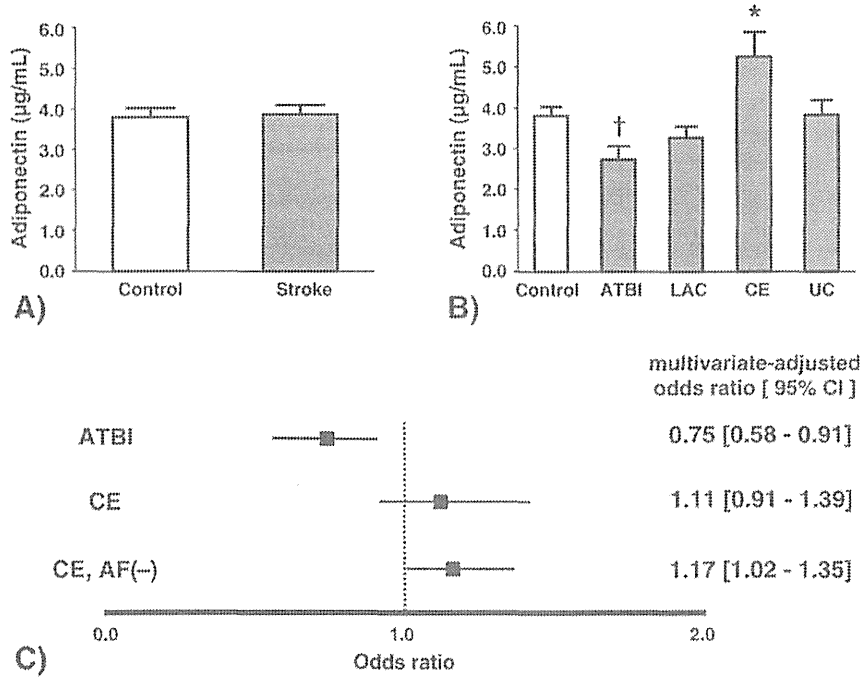

Fig. 1 – A) Plasma adiponectin values between all stroke patients at onset (day 0) and controls. Data are expressed as means ± SE. B) Plasma adiponectin values between each stroke subtype at onset (day 0) and controls. Data are expressed as means ± SE. *P < 0.01 and †P < 0.05 vs. control. C) Multivariate logistic regression analyses of plasma adiponectin values at day 0 as independent predictor of stroke subtypes, adjusting for age, gender, smoking habit, alcohol intake, hypertension, diabetes mellitus, atrial fibrillation, and neurological severity (NIHSS at day 0).

adiponectin value could be an independent predictor of CE in another model in which atrial fibrillation (AF), a powerful confounding factor for CE, was excluded from the adjustment factors (OR, 1.17; 95% CI, 1.02 to 1.35, p = 0.024, per 1 μg/mL increase; Fig. 1C). As shown in Table 4, the administration of β-blockers, diuretics or thiazolidinedione (model 2), insulin levels (model 3) or MetS (model 4) did not affect the statistical significance found in Fig. 1C (Table 4, model 1).

3.4. *Temporal profiles of plasma adiponectin values after stroke onset according to sex*

Fig. 2 shows temporal profiles of plasma adiponectin values according to sex for 90 days after stroke onset. Plasma adiponectin values were higher in stroke patients than in controls throughout the observational period with the statistical significance at day 0 and 90 in male patients. However,

Table 2 – Adiponectin values according to medications administered to patients.

	Controls n = 171			Patients n = 171		
	Drug (+)	Drug (–)	P	Drug (+)	Drug (–)	P
Antiplatelet, μg/mL (n)	(0)	3.8 ± 0.2 (171)		4.2 ± 0.4 (56)	3.7 ± 0.3 (115)	0.353
Anticoagulant, μg/mL (n)	(0)	3.8 ± 0.2 (171)		4.0 ± 0.7 (18)	3.9 ± 0.2 (153)	0.872
Antihypertensive, μg/mL (n)	4.3 ± 0.5 (40)	3.7 ± 0.3 (131)	0.238	4.2 ± 0.3 (104)	3.4 ± 0.4 (67)	0.094
Calcium-channel blockers, μg/mL (n)	4.6 ± 0.6 (25)	3.7 ± 0.2 (146)	0.156	4.1 ± 0.4 (74)	3.7 ± 0.3 (97)	0.342
ARB, μg/mL (n)	4.9 ± 0.7 (18)	3.7 ± 0.2 (153)	0.103	3.5 ± 0.4 (56)	4.0 ± 0.3 (115)	0.298
β-blockers, μg/mL (n)	2.0 ± 1.7 (3)	3.8 ± 0.2 (168)	0.301	2.7 ± 0.6 (23)	4.1 ± 0.2 (148)	0.046
Diuretics, μg/mL (n)	4.9 ± 1.7 (3)	3.8 ± 0.2 (168)	0.511	6.2 ± 0.6 (23)	3.5 ± 0.2 (148)	< 0.001
HMG-CoA reductase inhibitor, μg/mL (n)	4.8 ± 1.1 (8)	3.8 ± 0.2 (163)	0.339	3.6 ± 0.5 (31)	3.9 ± 0.3 (140)	0.563
Oral antidiabetic drugs, μg/mL (n)	7.5 ± 3.0 (1)	3.8 ± 0.2 (170)	0.216	3.4 ± 0.5 (32)	4.0 ± 0.3 (139)	0.311
Sulfonylurea, μg/mL (n)	(0)	3.8 ± 0.2 (171)		3.1 ± 0.6 (24)	4.0 ± 0.2 (147)	0.169
α-Glucosidase inhibitors, μg/mL (n)	(0)	3.8 ± 0.2 (171)		3.0 ± 0.7 (17)	4.0 ± 0.2 (154)	0.189
Metformin, μg/mL (n)	(0)	3.8 ± 0.2 (171)		2.7 ± 1.1 (7)	3.9 ± 0.2 (164)	0.315
Thiazolidinedione, μg/mL (n)	7.5 ± 3.0 (1)	3.8 ± 0.2 (170)	0.216	6.3 ± 1.2 (6)	3.8 ± 0.2 (165)	0.048
Insulin, μg/mL (n)	(0)	3.8 ± 0.2 (171)		4.9 ± 1.1 (8)	3.8 ± 0.2 (163)	0.328

Adiponectin values are shown as means ± SE. ARB, angiotensin receptor blocker.

Table 3 – Adiponectin values according to metabolic syndrome.

	MetS (+) (n = 70)	MetS (−) (n = 272)	P
Total study population, μg/mL (n)	3.3 ± 0.4 (70)	4.0 ± 0.2 (272)	0.084
Controls, μg/mL (n)	2.4 ± 0.7 (18)	4.0 ± 0.2 (153)	0.042
Stroke patients, μg/mL (n)	3.6 ± 0.4 (52)	4.0 ± 0.3 (119)	0.397
ATBI, μg/mL (n)	2.6 ± 0.6 (11)	2.8 ± 0.4 (23)	0.845
LAC, μg/mL (n)	2.9 ± 0.5 (15)	3.5 ± 0.4 (30)	0.329
CE, μg/mL (n)	4.6 ± 1.1 (15)	5.5 ± 0.7 (34)	0.498
UC, μg/mL (n)	4.1 ± 0.7 (11)	3.8 ± 0.4 (32)	0.709

Adiponectin values are shown as means ± SE. ATBI, atherothrombotic brain infarction; CE, cardioembolic infarction; LAC, lacunar infarction; MetS, metabolic syndrome; UC, unclassified type of brain infarction.

plasma adiponectin levels were rather lower in female patients than in female controls with the statistical significance at day 3, 7, and 14 after stroke onset.

3.5. *Temporal profiles of plasma adiponectin, cholesterol, and C-reactive protein levels after stroke onset*

Fig. 3A–D shows the comparisons of the temporal profile of plasma adiponectin values with that of total cholesterol, LDL cholesterol, HDL cholesterol and C-reactive protein after stroke for 90 days. The temporal profiles of total and LDL cholesterol were similar to that of adiponectin (Fig. 3A, B). In contrast, C-reactive protein values appeared to vary inversely with plasma adiponectin values within 90 days after stroke onset (Fig. 3D).

3.6. *Temporal profile of plasma adiponectin values after stroke onset according to stroke subtypes*

Fig. 4 shows temporal profiles of adiponectin values in each stroke subtype within 90 days after stroke onset. A decrease in plasma adiponectin values persisted for 90 days in ATBI with the statistical significance at day 0, 3, 7 and 14. In contrast, adiponectin values were higher throughout the same period in CE with the statistical significance at day 0 and 3. Adiponectin values in patients with LAC and UC did not significantly differ from those of the controls.

3.7. *Association between plasma adiponectin values and neurological severity*

We examined the association between plasma adiponectin values with neurological severity at day 0 in each stroke subtype. The median NIHSS score upon admission was 4 (interquartile range (IQR): 2–7) for all patients, and 4 (IQR: 2–8) for ATBI, 3 (IQR: 1–4) for LAC, 7 (IQR: 3–12) for CE and 4 (IQR: 2–6) for UC. Patients were assigned to groups Q1, Q2, Q3, and Q4 (in order of increasing severity) according to NIHSS upon admission in total stroke (Fig. 5A) and each stroke subtype (Fig. 5B–E). Adiponectin values correlated with neurological severity in all patients ($r = 0.420$, $p = 0.003$, Fig. 5A). The Q1 group in ATBI had significantly lower adiponectin values than controls (1.7 ± 0.3 vs. 3.8 ± 0.2 μg/mL, $p = 0.043$, Fig. 5B). On the other hand, the Q3 (5.8 ± 1.0 μg/mL, $p = 0.041$) and Q4 (6.5 ± 1.3 μg/mL, $p = 0.004$) groups in CE had significantly higher adiponectin values than the controls (3.8 ± 0.2 μg/mL) (Fig. 5D). Regardless of stroke subtypes, the higher the neurological severity was, the higher plasma adiponectin values tended to be (Fig. 5B–E).

3.8. *Association of plasma adiponectin values with functional outcome*

Adiponectin values at day 0 were significantly higher in the patients with poor functional outcomes (mRS ≥ 3 at day 90) than in those with good ones (mRS ≤ 2 at day 90) in total stroke patients (5.0 ± 0.6 vs. 3.5 ± 0.2 μg/mL, $p = 0.007$; Fig. 6A). They were also higher in the groups with poor outcomes in all stroke subtypes (Fig. 6B–E) with the statistical significance in ATBI (3.9 ± 0.9 vs. 2.1 ± 0.2 μg/mL, $p = 0.015$; Fig. 6B).

4. Discussion

4.1. *Clinical significance of plasma adiponectin values in subtype classification of ischemic stroke*

Some recent large case–control studies, including one investigation of postmenopausal women [22], have demonstrated that adiponectin levels are not independently

Table 4 – Multivariate logistic regression analyses of plasma adiponectin values as independent predictors of stroke subtypes.

	Model 1		Model 2		Model 3		Model 4	
	OR [95% CI]	P	OR [95% CI]	P	OR [95% CI]	P	OR [95% CI]	P
ATBI	0.75 [0.58–0.91]	0.009	0.75 [0.58–0.93]	0.018	0.75 [0.59–0.92]	0.011	0.75 [0.58–0.91]	0.009
CE	1.11 [0.91–1.39]	0.321	1.21 [0.96–1.57]	0.124	1.11 [0.91–1.38]	0.337	1.11 [0.91–1.39]	0.311
CE, AF(−)	1.17 [1.02–1.35]	0.024	1.29 [1.10–1.54]	0.003	1.17 [1.03–1.35]	0.023	1.17 [1.02–1.35]	0.024

The multivariate model 1 included age, sex, smoking habit, alcohol intake, hypertension, diabetes mellitus, atrial fibrillation, neurological severity (NIHSS upon admission).
Multivariate model 2 included same variables as model 1 and β-blockers, diuretics and thiazolidinedione.
Multivariate model 3 included same variables as model 1 and insulin.
Multivariate model 4 included same variables as model 1 and metabolic syndrome (MetS).
AF, atrial fibrillation; ATBI, atherothrombotic brain infarction; CE, cardioembolic infarction; CI, confidence interval; OR, odds ratio.

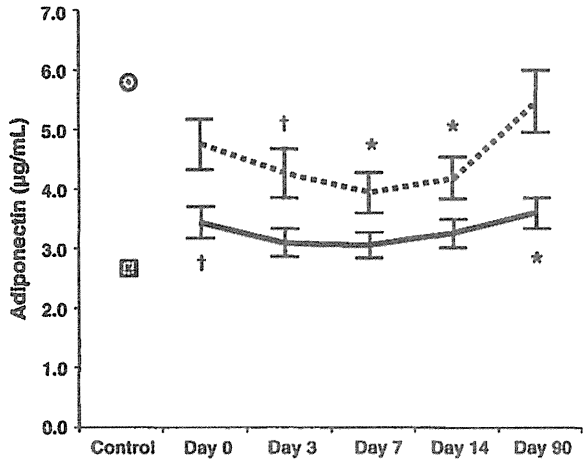

Fig. 2 – Temporal profiles of plasma adiponectin levels in male (solid line) and female (dotted line) patients for 90 days after stroke onset. ■, male controls; ●, female controls. Data are expressed as means ± SE. *P < 0.01 and †P < 0.05 vs. respective controls.

associated with stroke events [12,13,22]. One concern regarding these findings might be that the adiponectin values were not evaluated according to stroke subtypes. In contrast to ischemic heart disease, ischemic stroke is heterogeneous in its pathogenesis and can be classified into at least four (ATBI, CE, LAC and UC) subtypes, each of which occurs on different backgrounds. The pathogenesis of ATBI is similar to that of ischemic heart disease, and thus ATBI often arises in obese individuals with insulin resistance, whereas CE is more prevalent among aged individuals with atrial fibrillation. Because adiponectin values are closely associated with age, body mass index, and insulin resistance [10], heterogeneous backgrounds can cause heterogeneity in adiponectin values among stroke subtypes. In addition, the frequency of stroke subtypes might differ among ethnic groups. The frequency of stroke subtypes in various study populations might affect whether or not adiponectin is associated with ischemic stroke. Patients with ATBI seemed to predominate in several studies that found an inverse association between plasma adiponectin levels and risk of ischemic stroke, and genetic variations in the adiponectin gene that result in low adiponectin concentrations in plasma were associated with ischemic stroke [23–25].

To the best of our knowledge, few studies have investigated the significance of plasma adiponectin values in subtypes of ischemic stroke. A notable finding of the present study is that plasma adiponectin values were significantly lower in patients with ATBI, while higher in CE, than in controls, although the average values of all stroke patients were not different from those of controls (Fig. 1). These findings may be clinically useful because a differential diagnosis between ATBI

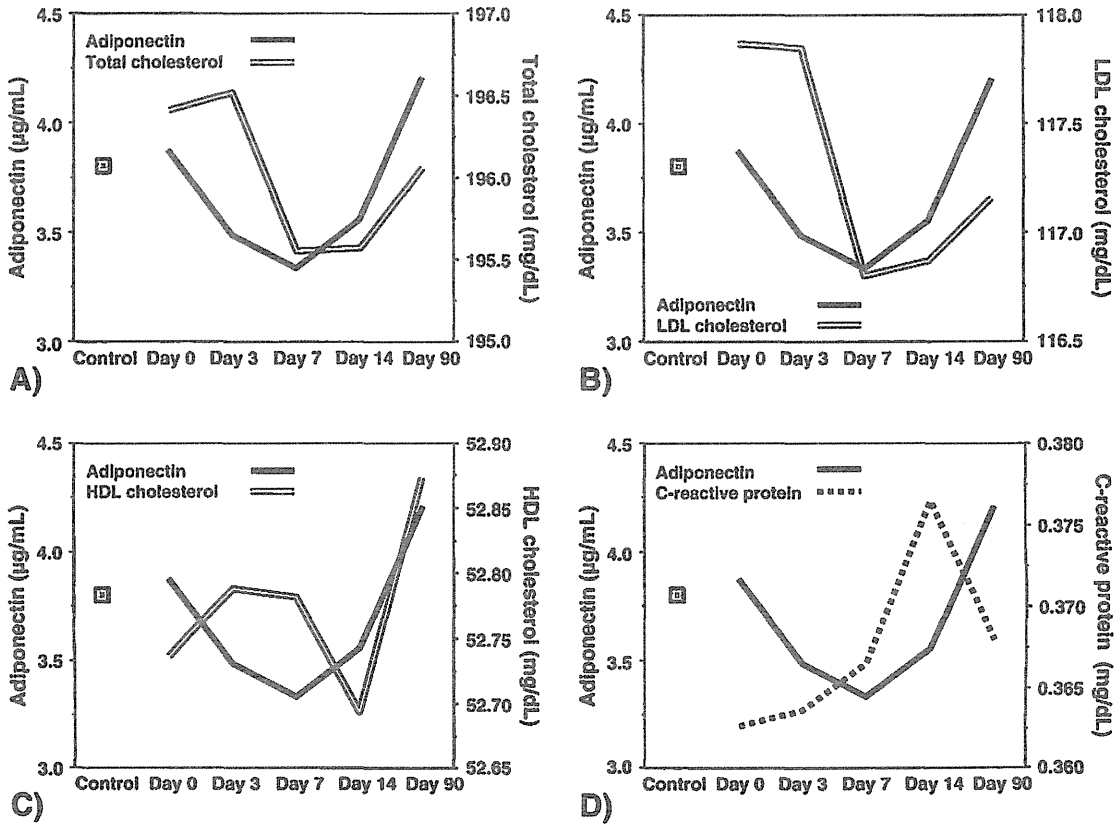

Fig. 3 – Temporal profiles of plasma adiponectin values and time course trends for cholesterol and C-reactive protein levels during first 90 days after stroke onset. ■, adiponectin levels of controls. Data are expressed as means.

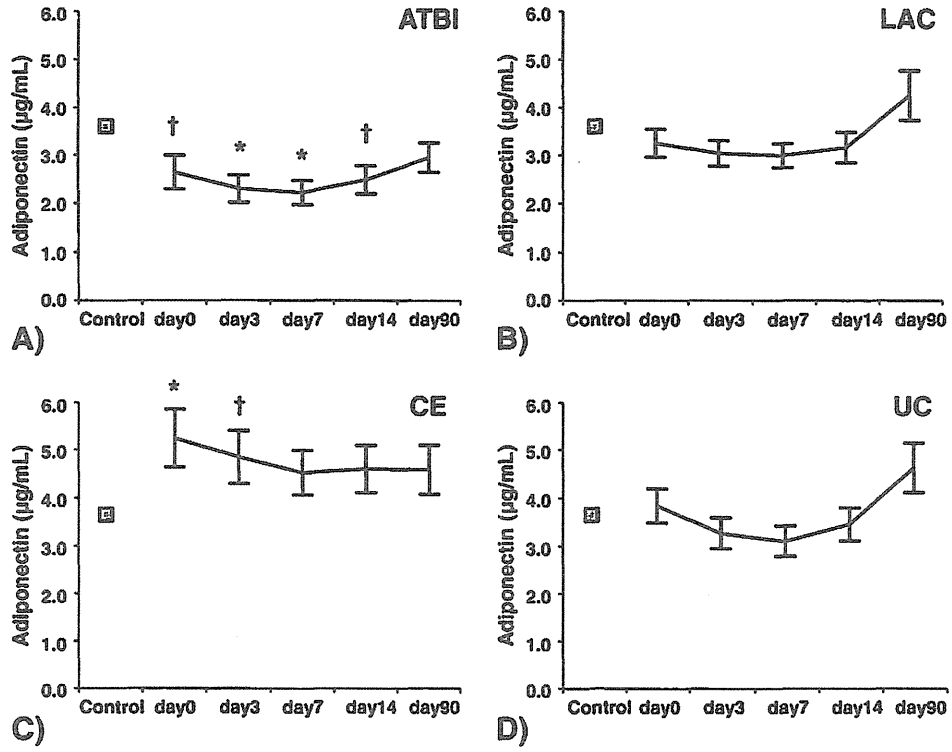

Fig. 4 – Temporal profiles of plasma adiponectin levels for 90 days after onset of each stroke subtype. A, ATBI; B, LAC; C, CE; D, UC. ▫, adiponectin levels of controls. Data are expressed as means ± SE. *P < 0.01 and †P < 0.05 vs. control.

and CE is absolutely required for appropriate therapies during the acute phase and for secondary prevention.

We consider that the difference in plasma adiponectin values between ATBI and CE at stoke onset may simply reflect patient background rather than the consequence of brain infarction. Adiponectin increases insulin sensitivity, stimulates the production of nitric oxide, and suppresses the expression of inflammatory cytokines and adhesion molecules in endothelial cells, thus maintaining endothelial functions and inhibiting the development of atherosclerosis [26–29]. Thus, chronic hypoadiponectinemia can cause the development and progression of atherosclerosis leading to ATBI. On the other hand, it has been reported that plasma adiponectin values are elevated in patients with chronic heart failure (CHF) [30] and atrial fibrillation (AF) [31], but lower in patients with ischemic heart diseases [7,8,32]. Since CHF and AF are major causes of CE, plasma adiponectin values may be higher in patients who are predisposed to CE.

4.2. *Adiponectin levels and neurological severity in patients with stroke*

Another notable finding of the present study is that plasma adiponectin values were higher in patients with neurologically severer deficits in each stroke subtype, particularly ATBI and CE (Fig. 5). There are two possible explanations: 1) adiponectin may contribute to the deterioration of neurological function in such patients, or 2) adiponectin may be elevated in response to brain ischemia to minimize damage. It has been reported that brain ischemia elicited a transient elevation in plasma adiponectin levels and circulating adiponectin accumulated in damaged vessels of mouse stroke models that mimic CE in humans [33], and promoted angiogenic repair [34,35]. Consistent with the findings in these animal models, plasma adiponectin values were significantly higher during the acute phase (day 0 and 3) in patients with CE in the present study. Thus, adiponectin may be produced in response to brain ischemia, and if so, could serve as a marker of neurological severity in brain infarction. Further studies are needed to clarify the roles of adiponectin in acute ischemic stroke in humans.

4.3. *Adiponectin levels and functional outcomes in patients with stroke*

High plasma levels of adiponectin comprise an independent predictor of mortality in patients with stroke [32], CHF [36], coronary heart disease [37] and chronic kidney disease [38]. We similarly found that the patients with poor functional outcomes had higher adiponectin values across all stroke subtypes, particularly ATBI (Fig. 6). The association between plasma adiponectin values and functional outcomes may simply reflect the association between these values and neurological severity upon admission. Adiponectin directly stimulates nitric oxide production in endothelial cells and plays beneficial roles on cerebral blood flow and infarct size [5,10,39]. Therefore, adiponectin might be produced in response to the extent of neurological injuries and thus might be higher in patients with severe neurological damage and poor outcomes. Alternatively, the association might explain the concept of the "obesity paradox" in ischemic stroke, which

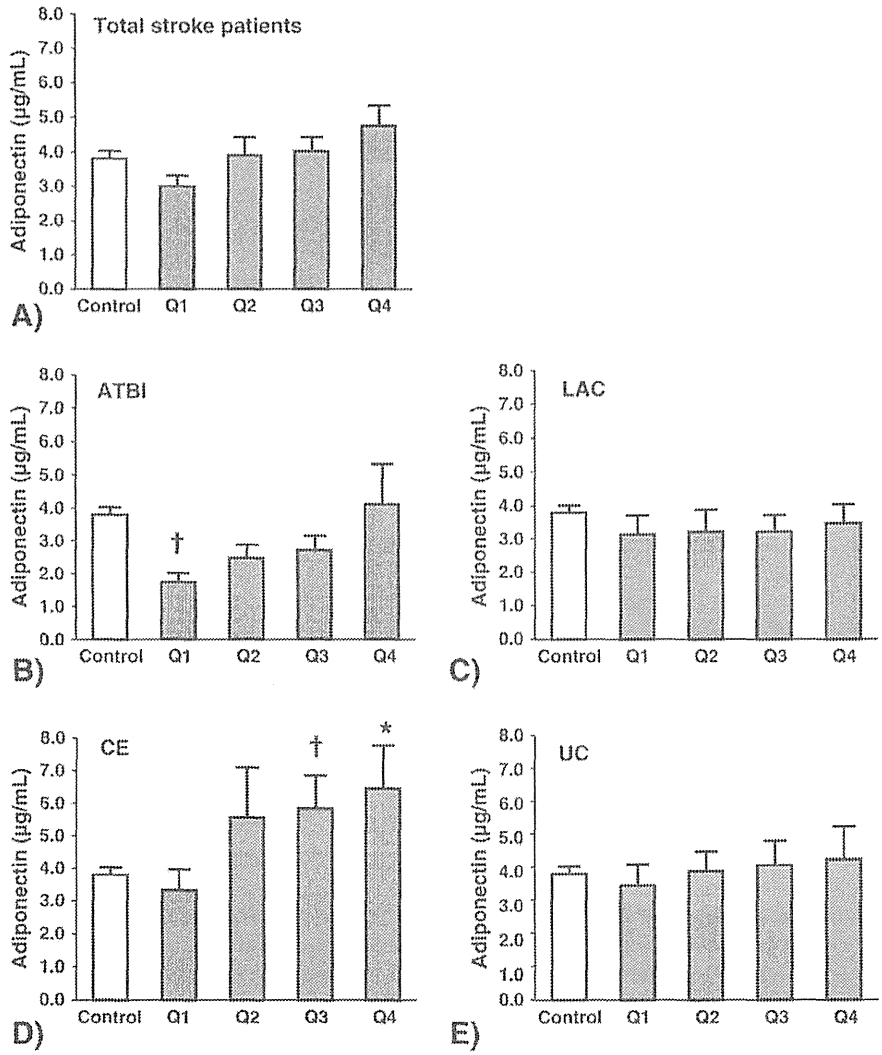

Fig. 5 – Association between plasma adiponectin values and neurological severity. A, All stroke patients; B, ATBI; C, LAC; D, CE; E, UC. Patients were assigned to Q1, Q2, Q3 and Q4 in order of increasing severity according to NIHSS upon admission. Data are expressed as means ± SE. *P < 0.01 and †P < 0.05 vs. control.

states that obese patients with various cardiovascular diseases [40,41], including ischemic stroke [42], have a better prognosis, although obese patients are undoubtedly predisposed to ischemic heart and brain diseases. Since adiponectin values are negatively associated with body mass index [36], obese stroke patients with low adiponectin values might have better functional outcomes.

4.4. *Temporal profiles of plasma adiponectin values after stroke onset*

We demonstrated that plasma adiponectin values were higher in women than in men in both healthy controls and stroke patients (Fig. 2), consistent with previous reports [43,44]. However, it has not been fully understood why adiponectin values are different between men and women [45]. Furthermore we found increases in plasma adiponectin levels in male, but decreases in female patients, after stroke onset. These trends lasted at least for 90 days after stroke onset in both sexes, although the mechanisms remain obscure.

It has been reported that cholesterol and adiponectin levels decrease after stroke onset [46,47]. We also found that they tended to decrease during the acute phase (Fig. 3). However, both cholesterol and adiponectin values increased later than the sub-acute phase, which might have been due to improved nutritional status in the later phase.

We compared the temporal profiles between C-reactive protein and adiponectin levels after stroke onset, and found that they appeared to vary inversely (Fig. 3). These findings may be consistent with the significant association between lower levels of adiponectin and higher levels of C-reactive protein often found in obese individuals [48,49].

We also showed the temporal profiles of plasma adiponectin values according to stroke subtypes. Consistent with a previous study that found a decrease in plasma adiponectin levels during the acute phase of cerebral infarction [46], we found similar decreases during the first 7 days after the onset

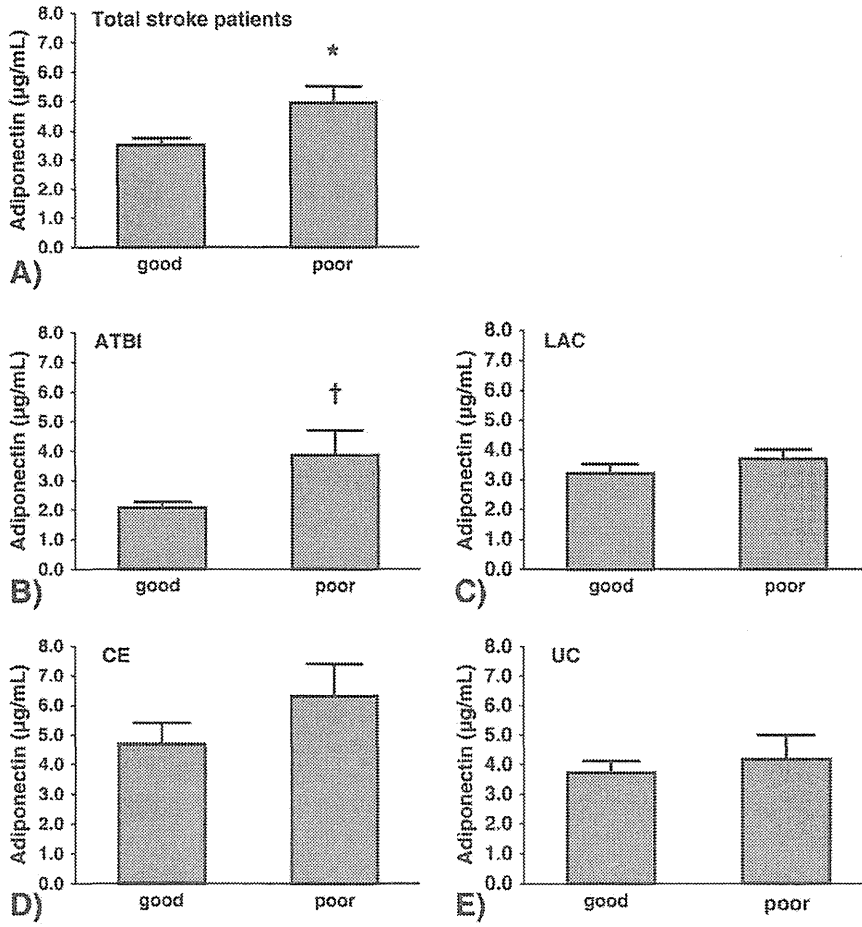

Fig. 6 – Associations between plasma adiponectin values at day 0 and good (mRS ≤ 2) or poor (mRS ≥ 3) functional outcomes at 90 days after stroke onset. A, All stroke patients; B, ATBI; C, LAC; D, CE; E, UC. Data are expressed as means ± SE. *P < 0.01 and †P < 0.05 vs. good group.

of all stroke subtypes (Fig. 4). In particular, plasma adiponectin values remained lower among patients with ATBI than controls for 90 days after stroke onset. A previous study, in which large artery atherosclerosis was the cause in about half of them, reported similarly that adiponectin levels remained decreased for 6 months after ischemic stroke [47].

4.5. *Study limitations*

The sample size was relatively small and the follow-up period might not be long enough to draw concrete conclusions. The small control group might have decreased statistical power. We plan to increase the size of the control group and review the present data in a larger population. The control group might have had background characteristics that differ from those of stroke patients and affect plasma adiponectin values. Because we did not measure plasma adiponectin values in the patients before stroke onset, we cannot conclude that the changes in plasma adiponectin values in the patients were a cause or an effect of stroke as discussed in Section 4.2. In addition, only survivors of ischemic stroke were enrolled in the present study. Plasma adiponectin levels in patients with fatal stroke might differ from those of survivors.

4.6. *Conclusions*

In the present study, we categorized patients according to stroke subtypes and examined the temporal profiles of plasma adiponectin values in each subtype. Despite some limitations, the present study indicates that plasma adiponectin values may be useful for classifying stroke subtypes and for predicting functional outcomes, particularly in ATBI and CE. Thus, measuring plasma adiponectin values would help us to classify stroke subtypes and to perform appropriate therapies for ischemic stroke. Furthermore, effective long-term strategies for treating stroke could be designed by predicting functional outcomes of stroke patients. Larger cohort studies are needed to confirm these findings.

Author contributions

T. Kuwashiro and T. Ago contributed to drafting the manuscript for content, study concept, analysis of data, acquisition of data, and statistical analysis. M. Kamouchi, R. Matsuo and J. Hata contributed to the study concept, and analysis and acquisition of data. J. Kuroda, K. Fukuda, H. Sugimori and

M. Fukuhara contributed to the study concept and acquisition of data. H. Awano, T. Isomura, K. Suzuki, M. Yasaka, Y. Okada, Y. Kiyohara and, T. Kitazono contributed to the study concept and study supervision.

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Conflict of interest

None to declare.

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ORIGINAL ARTICLE—ALIMENTARY TRACT

Risk factor profiles, drug usage, and prevalence of aspirin-associated gastroduodenal injuries among high-risk cardiovascular Japanese patients: the results from the MAGIC study

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Abstract
Background Low-dose aspirin is widely used for the prevention of cardiovascular events. The prevalence of gastroduodenal injuries and the risk factor profile including gastroprotective drug therapy needs to be clarified in Japanese patients taking daily aspirin for cardioprotection.
Methods This Management of Aspirin-induced Gastro-Intestinal Complications (MAGIC) study was conducted with a prospective nationwide, multicenter, real-world registry of Japanese patients at high-risk of cardiovascular diseases who were taking regular aspirin (75–325 mg) for 1 month or more. All patients underwent endoscopic examination for detection of gastroduodenal ulcer and mucosal erosion. The risk factor profiles including the concurrent drug therapy were compared for those patients with gastroduodenal problems and those without.
Results Gastroduodenal ulcer and erosion were detected in 6.5, and 29.2 % of the 1,454 patients receiving aspirin, respectively. *H. pylori* infection was associated with an increased risk for ulcer: OR 1.83 (1.18–2.88 $p = 0.0082$). Risk of erosion was lower with enteric-coated aspirin than with buffered aspirin: odds ratio (OR) 0.47 (0.32–0.70, $p = 0.0002$). Patients receiving proton pump inhibitors had lower risks for both gastroduodenal ulcer and erosion: OR 0.34 (0.15–0.68, $p = 0.0050$) and 0.32 (0.22–0.46, $p < 0.0001$), respectively. However, those receiving histamine 2-receptor antagonists had reduced risks for erosion but not for ulcer: OR 0.49 (0.36–0.68, $p < 0.0001$).

The MAGIC Study Group: Management of Aspirin-induced Gastrointestinal Complications.

Trial registration: UMIN000000750.

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Conclusion Gastroduodenal ulcer and erosion are common in Japanese patients taking low dose aspirin for cardioprotection. Proton pump inhibitors reduce the risk of gastroduodenal mucosal injury.

Keywords Low-dose aspirin · Gastroduodenal ulcer · Gastroduodenal erosion · Endoscopy · Cardiovascular patients

Introduction

Antiplatelet drug therapy reduces the risk of cardiovascular (CV) diseases in various patient populations. Aspirin use is supported with clinical evidence [1–3], but can cause adverse events, such as gastrointestinal (GI) injuries, even with a low-dose regimen [4]. According to meta-analyses, aspirin therapy increases the risk of GI bleeding by 2.7-fold as compared with results for a control arm, while it reduces the risk of major CV events by approximately 20 % [5]. These complications of GI bleeding are more complex than previously thought. Indeed, the risk of CV events increases in patients who have experienced major bleeding events within a year. Thus, GI bleeding may lead to a higher incidence of subsequent thrombotic events. The American Heart Association (AHA) recommends the use of low-dose aspirin (75–325 mg) for patients having a 10-year CV-event risk of 10 % or greater [6]. The US Preventive Services Task Force also recommends prophylactic aspirin therapy to be limited to patients with a 5-year CV risk of 3 % or greater, claiming that prophylaxis may not be beneficial for patients at low CV-event risk because the net clinical benefit is not high enough [7].

A limited amount of data is available for calculating the net clinical benefit in Japanese patients. Although it may not be directly comparable, data of the Western populations have indicated the overall relative risk of upper GI complications was 2.2 to 3.1 times higher in aspirin users than in non-aspirin users [8], whereas the odds ratio (OR) of upper GI bleeding was 5.5 in Japanese aspirin users [9]. The higher risk of GI bleeding in Japanese patients might be due to the higher prevalence of *Helicobacter pylori* infection in the elderly and those who smoke tobacco [9, 10].

We conducted the Management of Aspirin-induced Gastrointestinal Complications (MAGIC) study to determine the prevalence of endoscopic gastroduodenal ulcer and erosion in Japanese patients receiving regular aspirin for cardioprotection, and to clarify the risk factor profile including the concurrent use of gastroprotective drugs. This paper reports the baseline data obtained at the entry of this study.

Methods

Study design

This MAGIC study was conducted as an observational study in Japan. The details of the study design were published elsewhere [11]. Described briefly, the study consisted of high-risk CV patients taking low-dose aspirin for cardioprotection that were consecutively recruited from 63 nationwide institutions between April 2007 and September 2009. It was each investigator's discretion to judge "high risk of CV patients". Gastroduodenal ulcers and erosions were detected by endoscopy at enrollment. The study protocol was approved by the institutional review board in each institution. All participants signed the written informed consent. The present paper reports the baseline data of the enrollment.

Study population

The study population included patients with CV disease taking aspirin (75–330 mg daily) for at least 1 month. It included participants aged 20 years or older, and excluded those with serious hepatic, renal or pulmonary disorders, active cancer, hypersensitivity to aspirin or salicylate derivatives, pregnancy, possible pregnancy or pregnancy being planned, and prior surgical resection of esophagus, stomach, or duodenum.

Baseline demographic information

Upon the study entry, data on each patient's age, sex, underlying CV disease (e.g., coronary artery disease, cerebrovascular disease, and atrial fibrillation), comorbidities (hypertension, hyperlipidemia, diabetes mellitus, and metabolic syndrome), smoking habit, alcohol and coffee consumption, aspirin dosage and formulations (buffered or enteric coated), use of concomitant drugs, and history of upper GI ulcer were collected. All the participants were tested for the presence of *H. pylori* antibody after signing informed consent. *H. pylori* antibody in blood sample was measured using Anti-*H. pylori* IgG assay kit (SRL Inc., Tokyo, Japan). The *H. pylori* antibody was considered positive if the antibody level was $\geq$10 U/mL. The information on history of *H. pylori* eradication was collected from the patient medical records, where the eradication therapy was not well defined. Therefore, the results of eradication therapy were excluded from analysis. Antiulcer drugs included proton pump inhibitors (PPI), histamine 2-receptor antagonists (H2RA), cytoprotective antiulcer drugs, or prostaglandin analog (PGA).

Endoscopic assessment

Gastroduodenal ulcers or erosions were detected by endoscopy and the diagnosis was confirmed by the endoscopic evaluation committee (see Appendix). Gastroduodenal ulcer was defined by a mucosal break of 5 mm or greater in diameter with unequivocal depth, and erosion by mucosal change covered with white necrotic substance of less than 5 mm in diameter. The longer diameter of the lesion was measured as a standard of the length that opened biopsy forceps of 6 mm.

Study organization

The study design was formulated by the Organizing Committee (see Appendix), and data were collected through an Internet-based system.

Statistical analysis

Results were expressed as mean ± SD. Categorical variables between two groups were analyzed with Fisher's exact test, and the means of unpaired continuous variables, by Welch's t test. The prevalence and 95 % confidence interval (CI) were estimated by using the binomial distribution. The risk of gastroduodenal ulcer or erosion was estimated by the OR with 95 % CI by using univariate and multivariate logistic regression models. In the multivariate model, the odds ratio was adjusted by suspected risk factors such as age, sex, current tobacco smoking, alcohol use, diabetes mellitus, the presence of *H. pylori* antibody, and history of peptic ulcer, and uses of enteric-coated aspirin, PPI, H2RA, cytoprotective antiulcer drugs. A $p < 0.05$ was considered as statistically significant. Statistical analyses were performed by using the software R 2.14.0 (R foundation for Statistical Computing, Vienna, Austria).

Role of the funding source

The sponsor foundation had no role on the study design, selection of study institutions, selection of the committee members, data analyses, or the writing of the manuscript.

Results

Baseline characteristics of the patients

Among 1,531 patients who were consented and enrolled in the present study, 39 patients refused endoscopy and withdrew the consent, and remaining 1,492 patients received endoscopy. Data of 1,454 participants were used for analysis excluding those of 38 patients for gastric cancer, esophageal cancer, or colon cancer (Fig. 1).

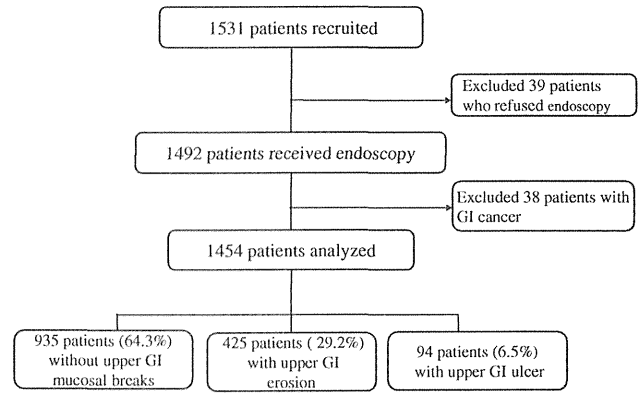

Fig. 1 Flow chart of the study patients

The mean participants' age was 68.1 ± 9.5 years, and 73.5 % of the participants were male. Aspirin was received daily for a mean duration of 4.6 ± 4.4 years (Table 1). A total of 89.4 % received enteric-coated aspirin and 10.6 %, buffered aspirin. The majority of the patients took 100 mg daily of enteric-coated aspirin (92.8 %), and 81 mg daily of buffered aspirin (96.2 %). Other NSAIDs were concomitantly used in only 6.5 %.

Baseline prevalence of gastroduodenal injury

The point prevalence of gastroduodenal ulcer was 6.5 % and erosion, 29.2 % (Table 1).

Among 94 patients with ulcer, the majority had gastric ulcer (80 cases, 85.1 %), following duodenal ulcer (10 cases, 10.6 %) and gastroduodenal ulcers (4 cases, 4.3 %).

Mean age was unexpectedly lower in the erosion (67.3 ± 9.3 years) and ulcer groups (65.1 ± 10.2 years) than in the group absent of mucosal break (AMB) (68.8 ± 9.5 years) ($p = 0.0060$ and $p = 0.0009$, respectively). In comparison with the AMB group, the ulcer group had greater proportions of male patients and current smokers ($p = 0.0103$ and $p = 0.0102$, respectively). The prevalence of diabetes mellitus was higher ($p = 0.0378$), and that of *H. pylori* antibody positive was lower only in the erosion group ($p < 0.0001$). Use of enteric-coated aspirin was significantly lower in the erosion group (84.9 %) and in the ulcer group (83.0 %) than in the AMB group (92.1 %) ($p = 0.0001$ and $p = 0.0063$, respectively).

Risk of gastroduodenal injury

According to risk analysis (Tables 2, 3), current smoking and *H. pylori* antibody positive were significant risk factors for ulcer: OR = 1.87 (1.03–3.25, $p = 0.0321$) and

Table 1 Baseline patient characteristics

	Total (n = 1454)	AMB (n = 935) (64.3 %)	Erosion (n = 425) (29.2 %)	p value[a]	Ulcer n = 94 (6.5 %)	p value[b]
Age (year)	68.1 ± 9.5	68.8 ± 9.5	67.3 ± 9.3	0.0060	65.1 ± 10.2	0.0009
Men (%)	1068 (73.5)	669 (71.6)	320 (75.3)	0.1678	79 (84.0)	0.0103
Body weight (kg)	62.6 ± 11.0	62.0 ± 11.1	63.3 ± 10.6	0.0522	64.4 ± 12.2	0.0722
Height (cm)	161.4 ± 8.5	160.9 ± 8.5	162.3 ± 8.4	0.0047	162.4 ± 7.9	0.0689
Body mass index (kg/m^2)	23.9 ± 3.2	23.9 ± 3.2	24.0 ± 3.1	0.6021	24.3 ± 3.4	0.2780
Underlying disease						
Cerebrovascular disease (%)	626 (43.1)	395 (42.2)	192 (45.2)	0.3160	39 (41.5)	0.9132
Coronary artery disease (%)	711 (48.9)	458 (49.0)	199 (46.8)	0.4825	54 (57.4)	0.1301
Atrial fibrillation (%)	155 (10.7)	108 (11.6)	41 (9.6)	0.3489	6 (6.4)	0.1662
Comorbidity						
Hypertension (%)	1053 (72.4)	674 (72.1)	306 (72.0)	1.0000	73 (77.7)	0.2763
Hyperlipidemia (%)	830 (57.1)	522 (55.8)	253 (59.5)	0.2148	55 (58.5)	0.6635
Diabetes mellitus (%)	416 (28.6)	249 (26.6)	137 (32.2)	0.0378	30 (31.9)	0.2749
Metabolic syndrome (%)	779 (53.6)	489 (52.3)	235 (55.3)	0.3192	55 (58.5)	0.2789
H. pylori antibody positive (%)	700 (48.1)	509 (54.4)	132 (31.1)	<0.0001	59 (62.8)	0.1546
Others concurrent disease (%)	650 (44.7)	429 (45.9)	180 (42.4)	0.2395	41 (43.6)	0.7448
Previous history of peptic ulcer (%)	311 (21.4)	202 (21.6)	83 (19.5)	0.4292	26 (27.7)	0.1925
Habit						
Current tobacco smoking (%)	151 (10.4)	100 (10.7)	32 (7.5)	0.0752	19 (20.2)	0.0102
Alcohol use (%)	591 (40.6)	364 (38.9)	181 (42.6)	0.2103	46 (48.9)	0.0611
Coffee consumption (%)	767 (52.8)	482 (51.6)	233 (54.8)	0.2663	52 (55.3)	0.5169
Aspirin use						
Enteric-coated aspirin (%)	1300 (89.4)	861 (92.1)	361 (84.9)	0.0001	78 (83.0)	0.0063
Duration of aspirin use (year)	4.6 ± 4.4	4.5 ± 4.4	4.7 ± 4.4	0.4679	5.0 ± 4.7	0.2924
Concomitant drug						
Other antiplatelet (%)	355 (24.4)	228 (24.4)	107 (25.2)	0.7860	20 (21.3)	0.6128
Anticoagulant (%)	175 (12.0)	125 (13.4)	43 (10.1)	0.1092	7 (7.4)	0.1077
Other NSAID (%)	94 (6.5)	60 (6.4)	31 (7.3)	0.5593	3 (3.2)	0.2642
Antihypertensive drug (%)	1084 (74.6)	701 (75.0)	312 (73.4)	0.5464	71 (75.5)	1.0000
Angiotensin II receptor blocker	754 (51.9)	478 (51.1)	219 (51.5)	0.4390	57 (60.6)	1.0000
Lipid-lowering drug (%)	753 (51.8)	478 (51.1)	219 (51.5)	0.9069	56 (59.6)	0.1299
HMG-Co A reductase inhibitor	682 (46.9)	430 (46.0)	201 (47.3)	0.6815	51 (54.3)	0.1303
Antidiabetic drug (%)	275 (18.9)	160 (17.1)	94 (22.1)	0.0297	21 (22.3)	0.2027

A total of 1454 participants were categorized into three groups by endoscopy: the group with absence of mucosal break (AMB), the group with gastroduodenal erosion (erosion), and the group with gastroduodenal ulcer (ulcer). The proportion of participants in each demographic category was examined among the three groups. Categorical variables were tested with Fisher's exact test and continuous variables with Welch's two sample t-test

AMB absence of mucosal break

[a] p value between AMB and erosion

[b] p value between AMB and ulcer

OR = 1.83 (95 % CI 1.18–2.88, p = 0.0082), respectively. However, a reduced risk of erosion was found with *H. pylori* antibody positive: OR = 0.34 (0.26–0.44, $p < 0.0001$), and a reduced risk of ulcer was found in the elderly population (>65 years old): OR = 0.60 (0.39–0.94, p = 0.0246). The risk for erosion but not for ulcer was significantly lower in use of enteric-coated aspirin (OR = 0.47, 0.32–0.70, p = 0.0002) than in use of buffered aspirin (OR = 0.57, 0.32–1.05, p = 0.0569).

In the analysis of 690 patients not treated with antiulcer drugs, the prevalence of ulcer and erosion were significantly lower with use of enteric-coated aspirin (7.8 and 33.5 %, respectively) than with use of buffered aspirin (12.8 and 47.4 %, respectively) (Fig. 2).